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Mescaline and LSD facilitate the activation of locus coeruleus neurons by peripheral stimuli

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As D-lysergic acid diethylamide (LSD) and mescaline (3,4,5-trimethoxyphenylethylamine) have similar effects on autonomic function and behavior[38], it has been assumed that these psychedelic drugs share a common site of action. Furthermore, in various species, cross tolerance occurs between LSD and mescaline[6,7]. A metabolic mechanism does not seem to account for this cross tolerance since prior treatment with mescaline does not reduce brain levels of LSD[37]. Several investigators have proposed that mescaline may assume a structural conformation resembling a portion of the LSD molecule, suggesting that LSD and mescaline may act on the same receptor site in the CNS[27,32,35]. However, tests of this hypothesis by single cell recording techniques have largely failed to demonstrate a common site of action. Systemically administered LSD inhibits the firing of serotonin (5-HT)-containing neurons of the raphe nuclei[1]; a similar inhibition is obtained when LSD is given locally by microiontophoresis[3]. In contrast, systemically administered mescaline does not consistently suppress the firing of 5-HT neurons[2] and it does not inhibit 5-HT neurons at all when it is applied directly by microiontophoresis[26]. On the other hand, a similarity between the direct actions of mescaline and LSD has been found on motoneurons where both drugs sensitize facilitatory effects of 5-HT and norepinephrine (NE)[30]. In the periphery, mescaline can have both agonist and antagonist actions at adrenergic receptors[17]. When applied to unidentified brain stem neurons, mescaline can block responses to catecholamines[23]. In the cerebral cortex, mescaline exerts both excitatory and depressant actions[9,12]; regardless of the direction of change, the effects of mescaline are correlated better with those of norepinephrine (NE) than those of 5-HT or LSD. Thus, in the cerebral cortex, mescaline and LSD do not seem to have common effects on presumed postsynaptic NE or 5-HT receptors.

Mescaline and LSD both induce a decrease in levels of NE in brain[8,20,29], suggesting a possible similarity of presynaptic action on NE neurons. In the present study, effects of mescaline and LSD on the firing of NE neurons of the locus coeruleus (LC) were examined; related drugs with known actions on the LC neurons (e.g. L-amphetamine, desipramine and clonidine) were also tested for purposes of comparison.

Unexpectedly, although mescaline and LSD were found to depress the spontaneous activity of LC neurons, they both caused an increase in the reactivity of LC neurons to the excitatory influences of peripheral stimuli.

Seventy-four male albino rats (Charles River) weighing 225–275 g were used. The animals were anesthetized with chloral hydrate (400 mg/kg, i.p.) and mounted in a stereotaxic instrument; a heating pad maintained body temperature at 36–37 °C. For the LC cell recordings, a burr hole was made 1.2 mm posterior to lambda and 1.1 mm lateral to the midline. As described previously[4,13–15,28], practical aids for locating the LC include: (1) the presence just lateral to the LC of cells of the mesencephalic nucleus of the fifth nerve which are activated by displacement of the mandible; and (2) in the LC itself, a closely-packed population of slowly firing cells all responding to noxious stimulation by a burst of firing followed by a long quiescent period. For histological confirmation of LC recording sites, the electrode tip locations were marked at the end of each experiment by iontophoretically ejected dye (Fast Green). Procedures for extracellular single-cell recording and microiontophoresis have been described previously[4,15]. To quantify responses to peripheral stimuli the sciatic nerve was stimulated through a bipolar electrode inserted in the nerve sheath and sutured in place as previously described[5]; responses were monitored by average rate recordings and post-stimulus-time histograms. Drugs were administered intravenously via a tail vein. Drug dosages are given in terms of the weight of the salt as follows: mescaline hydrochloric acid (Aldrich); D-lysergic acid diethylamide bitartrate (NIDA); methysergide maleate (Sandoz); L-amphetamine sulfate (Aldrich); clonidine hydrochloric acid (Boehringer-Ingelheim); and desipramine hydrochloric acid (USV Pharmaceuticals).

Intravenously administered mescaline produced a dose-dependent suppression of the spontaneous firing of LC neurons; the effective dose for 50% suppression of firing was 0.85 mg/kg (log–probit method; doses of 0.25, 0.5, 1.0 and 2.0 mg/kg; n = 5 animals/dose). LSD did not produce a dose-dependent decrease in LC firing. Indeed, previous studies have reported an activation of LC cells by relatively high doses of the drug (e.g. 25 μg/kg)[34,36]. However, in the present experiments, LC cells were not activated by low doses of LSD (5–10 μg/kg); instead, a prolonged partial suppression of firing developed several minutes after injection. Despite the reduction in baseline rate, both mescaline and LSD enhanced the reactivity of LC neurons to peripheral stimuli. After the injection of mescaline or LSD, responses could be elicited by innocuous stimuli (e.g. light stroking of fur on back or air puffs) which normally do not activate LC neurons in anesthetized animals[15]. Furthermore, responses to noxious stimuli were enhanced (e.g. pinching of skin). These effects were not shared by several other drugs which also depress the firing of LC neurons as follows: (1) L-amphetamine, which suppresses firing in part by releasing NE from inhibitory recurrent collaterals in the LC[4]; (2) desipramine, which suppresses LC firing by blocking NE uptake from such recurrent collaterals[4]; and (3) clonidine which acts directly on inhibitory (α 2 or presynaptic) adrenoceptors located on LC neurons[13,14,36]. As can be seen from Fig. 1, at the low currents which were used (0.1–0.2 μA) low frequency stimulation (0.25 Hz) of the sciatic nerve had no effect on the average rate of firing of LC neurons. However, when cell firing was suppressed by mescaline (Fig. 1, top trace),

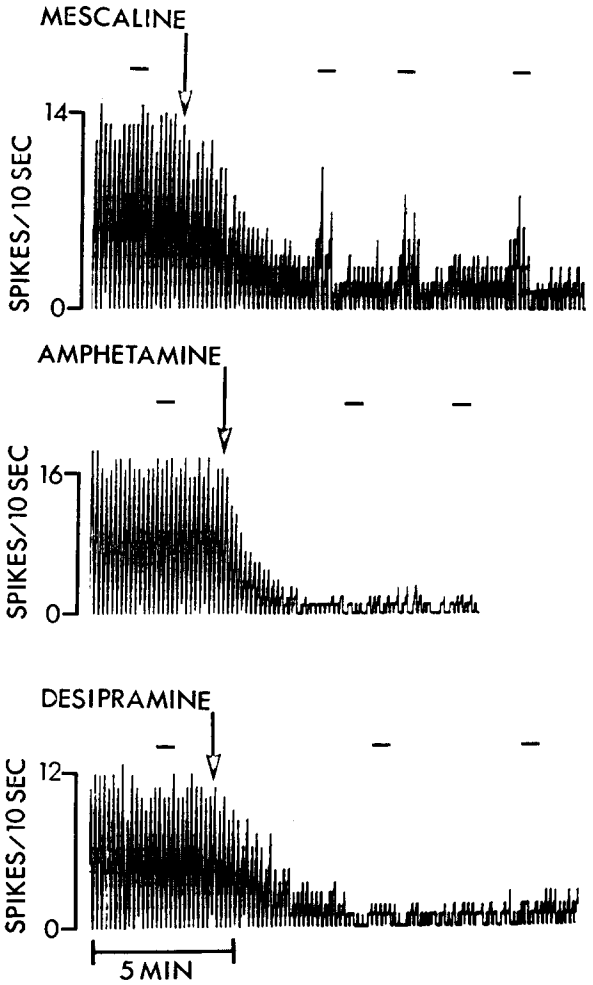

Fig. 1. Effects of mescaline, (—)-amphetamine and desipramine on average firing rate and responses to periods of sciatic nerve stimulation (bars) of locus coeruleus neurons. Drugs were given by slow i.v. infusion (arrows). Doses were as follows: mescaline, 2 mg/kg; (—)-amphetamine, 0.5 mg/kg; desipramine, 0.4 mg/kg. Note that the monophasic sciatic nerve stimulation (0.1–0.2 mA, 0.25 Hz) does not alter average rate prior to drug administration as activations which do occur in the pre-drug period are compensated for by an equivalent post-activation suppression in firing (see Fig. 2 and ref. 26). Although each of the 3 drugs induced a suppression of baseline firing, only after mescaline does nerve stimulation produce activations above baseline rate.

nerve stimulation was able to produce an overall acitvation. The duration of the enhanced reactivity was correlated with the period of depression in baseline firing rate (0.5–1 h). No LC cell activation was seen during periods of depressed firing induced by L-amphetamine (Fig. 1, middle trace), desipramine (Fig. 1, bottom trace), or clonidine (not shown). Post-stimulus time histograms (Fig. 2, Table I) reveal this difference even more clearly. After mescaline the number of spikes evoked by nerve stimulation is increased and the period of post-activation inhibition is prolonged (Fig. 2A); the effects of LSD are similar to those of mescaline (Fig. 2D). In contrast, after L-

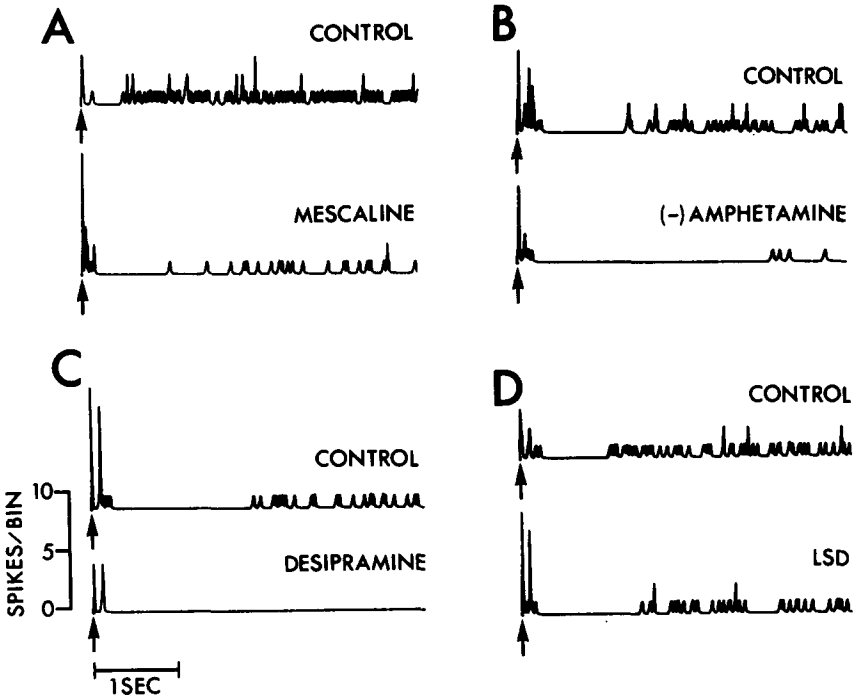

Fig. 2. Post-stimulus time histograms during locus coeruleus cell recordings before and after i.v. administration of mescaline, (—)-amphetamine, desipramine and LSD. Each histogram was generated from 10 sweeps initiated by sciatic nerve stimulations (arrows) delivered at 0.25 Hz (0.1–0.2 mA). A low frequency was used to avoid overlapping periods of post-activation inhibition. Note that only in the case of mescaline and LSD is there an increase in activations (initial 250 msec segment of histogram).

amphetamine, desipramine and clonidine evoked spikes are suppressed (Fig. 2, Table I). Methysergide, a non-psychedelic lysergic acid derivative, neither depressed spontaneous activity not enhanced evoked spikes in doses up to 1 mg/kg (n = 6 animals).

TABLE I

The effects of intravenous mescaline, LSD, (—)-amphetamine, desipramine and clonidine on baseline firing rate and evoked spikes in the locus coeruleus

Pre- and post-drug differences in evoked spikes were based on the first 250 msec segment of post-stimulus time histograms taken before and 4–6 min after drug administration. *P* values were determined by paired *t*-tests.

Drug (n = number of rats)	*Dose*	*% Change in baseline rate ± S.E.M.*	*% Change in evoked spikes ± S.E.M.*
Mescaline (n = 6)	2 mg/kg	—78 ± 3	+98 ± 30 ($P < 0.005$)
LSD (n = 6)	10 μg/kg	—37 ± 4	+41 ± 5 ($P < 0.001$)
(—)-Amphetamine (n = 6)	0.5 mg/kg	—83 ± 4	—38 ± 6 ($P < 0.01$)
Desipramine (n = 6)	0.4 mg/kg	—84 ± 3	—48 ± 9 ($P < 0.005$)
Clonidine (n = 6)	8 μg/kg	—87 ± 4	—22 ± 10 ($P < 0.05$)

This study shows that systemically administered mescaline and LSD enhance the reactivity of LC neurons to peripheral stimuli despite the fact that spontaneous activity is reduced. This represents one of the few demonstrations of a common action of these drugs on a single-cell level. In contrast, a number of other drugs which reduce spontaneous LC cell activity but which are non-psychedelic (e.g. L-amphetamine, desipramine and clonidine) failed to enhance responsivity to stimuli. The non-psychedelic LSD analogue methysergide was also ineffective. Previously it has been shown that both LSD and mescaline sensitize the facilitatory effects of 5-HT and NE on facial motoneurons[30]. Of course, such facilitatory effects on motoneurons are not likely to be involved in the hallucinogenic actions of mescaline and LSD. Nevertheless, it is possible that, as with motoneurons, the enhanced reactivity of LC neurons induced by mescaline and LSD represent a sensitization to excitatory afferent inputs. In preliminary studies, the excitation of LC neurons by microiontophoretically-applied acetylcholine, glutamate or substance P (see ref. 25) was not enhanced by systemic doses of mescaline or LSD which concomitantly enhanced responses to peripheral stimuli. Thus, the effects of mescaline and LSD appear to be mediated through an effect on LC afferents rather than directly through an increase in the excitability on LC neurons per se. Afferents to the LC which potentially could mediate responses to peripheral stimuli have been located in various sensory relay neurons of the spinal cord and the lower brain stem[16].

The present findings are reminiscent of earlier studies which have shown an activating effect of low doses of LSD on evoked potentials in specific sensory systems[33]. Moreover, the activation of EEG by LSD is enhanced by increased external stimuli[11]. Clinical reports similarly show that the subjective effects of LSD are accentuated with increased environmental stimulation[18,21]. Furthermore, the ECoG-activating effect of LSD differs from the stimulants such as amphetamine which activate the ECoG independently of the level of ambient stimulation[10]. More recently, it has been shown that LSD[19,31] and mescaline[22] enhance startle responses to acoustic and tactile stimuli, respectively. Thus, the mechanisms by which LSD or mescaline enhance the reactivity of NE neurons to peripheral stimuli may offer a clue to common neurophysiological actions underlying the psychedelic effects of these drugs.

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